Remarks

Reconsideration of this Application is respectfully requested.

Applicants wish to point out that contrary to the Office Action Summary, also claims 50 and 51 are pending in the application since only claims 13, 16, 27, 30, 40, 49, and 52-58 were canceled in the Amendment and Reply Under 37 C.F.R. § 1.111 filed July 12, 2002. Applicants respectfully request correction.

Upon entry of the foregoing amendment, claims 1-12, 14, 15, 17-26, 28, 29, 31-39, 41-48, 50, 51, and 59-71 are pending in the application, with claims 1, 2, 50, 63, 68, and 69 being the independent claims. Claims 1, 2, 50, 51, 63, and 68 are sought to be amended, and new claims 69-71 are sought to be added. Support for the amendments and new claims 69-71 can be found in the original specification and claims as filed. These changes are believed to introduce no new matter, and their entry is respectfully requested. Specifically, claims 1, 2, and 50 have been amended by requiring that each R_2 is hydrogen when R_1 is a carboxy group, X is O, A_1 is N, and Y is an optionally substituted phenyl group. Support for these amendments can be found in the examples of the original specification: the only pyrimidine compound exemplified that has a carboxy group in the 2-position of the pyrimidine ring does not have any other substituent attached to the pyrimidine ring but an optionally substituted phenyl-O-phenyl (*See* Example 1d in paragraph [0157] at page 43 of the specification as filed). Claim 51 has been amended by amending the dependencies. Claims 63 and 68 have been amended to be independent claims. In addition, claims 63 and 68 have been amended by canceling the phrase "alkylcarbonylamino, arylcarbonylamino" from the definitions for the substituent R_2.

New claim 69 is supported by claim 1 as originally filed. Claim 69 differs from claim 1 by not including "O" as a definition for X when Y is an optionally substituted phenyl group. New claims 70 and 71 are supported by claim 2 as originally filed. Claim 70 is directed to compounds of Formula II where A_1 is N, and differs from claim 2 by

not including "hydrogen" as a definition for R_9 thereby excluding –C(O)OH from the definitions for R_1. Claim 71 is directed to compounds of Formula III where A_3 is N. Applicants submit that no new matter has been introduced by new claims 69-71 and by amendments to claims 63 and 68 since deletion of individual members of Markush expression does not constitute new matter. See, *In re Johnson and Farnham*, 194 U.S.P.Q. 187 (CCPA 1977).

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-12, 14, 15, 17-26, 28-29, 31-39, 41-48 and 59-68 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse this rejection.

The Examiner again alleges that the term "prodrug" in claims 1, 2, 17, 31, and 50 is indefinite. The Examiner states that the "issue is what is difference between the groups already recited in the variable definition and those recited as prodrug."

Applicants respectfully disagree and submit that the term "prodrug" is not indefinite. Compounds of the invention containing the groups already recited in the variable definition may or may not include prodrugs, depending on the capability of the group to undergo *in vivo* metabolism, such as hydrolysis. A person skilled in the art would know which various R groups defined in independent claims 1, 2, and 50 would be able to act as prodrugs.

Further, there is no *per se* rule that a double inclusion is improper in a claim. The mere fact that a compound may be embraced by more than one member of a Markush group recited in the claim does not lead to any uncertainty as to the scope of that claim for either examination or infringement purposes. *See* M.P.E.P. § 2173.05(o).

Furthermore, for example, even though "halogen" is generic to "chloro" the Markush group "selected from the group consisting of amino, halogen, nitro, chloro and alkyl" is acceptable. *See* M.P.E.P. § 2173.05(h). Applicants respectfully submit that one skilled in the art would be able to ascertain the scope of protection defined by the pending claims with regard to the term "prodrug" and, therefore, request that the rejection of claims 1, 2, 17, 31, and 50 be withdrawn. Applicants wish to point out that claims 62 and 67 do not recite the term "prodrug."

Further, the Examiner alleges that

> [c]laims recite "aminocarbonyl" group and "carboxamido" group that render these claims indefinite as it is not clear what is the difference. It implies more than what is positively recited in either of the group.

(Office Action, page 3, lines 4-6).

Applicants disagree. Applicants reviewed the claims but could not locate any recitation of the word "carboxamido." Thus, Applicants assume the Examiner intended to use the word "carboxamide" instead of "carboxamido" as recited in claims 39, 59, and 60. There is no difference between the terms "aminocarbonyl" and "carboxamide." The specification as filed describes in paragraph [0090] at page 19, that "aminocarbonyl" group is $-C(O)NH_2$. It is known in the art that the "aminocarbonyl" group is the same as the "carboxamide" group as recited in claims 39, 59, and 60. Support for this can be found from the specification as filed, *inter alia*, in examples 17 and 18.

In view of the above, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, of claims 1-12, 14, 15, 17-26, 28-29, 31-39, 41-48 and 59-68 are respectfully requested.

Rejection under 35 U.S.C. § 102(b)

Applicants acknowledge with appreciation that the Examiner has withdrawn the rejections under 35 U.S.C. § 102(b) over Kim *et al.* (U.S. Pat. No. 3,631,036) and Hepworth *et al.* (U.S. Pat. No. 3,502,673).

The Examiner has rejected claims 1, 50-51, and 61-68 under 35 U.S.C. § 102(b) as allegedly being anticipated by Tsutomu *et al.* (GB 2,095,240). Applicants respectfully traverse this rejection.

The Examiner states that

> Applicants' argument to overcome this rejection is not persuasive as "the oxo" group in the ring is a tautomer of instant hydroxyl. Hence the rejection is maintained.

(Office Action, page 3, lines 1-2 from the bottom of the page).

Applicants respectfully disagree. It is respectfully submitted that Tsutomu *et al.* do not describe any compound or pharmaceutical composition that falls into the scope of independent claim 1, 50, 63, or 68.

The abstract of Tsutomu *et al.* recites that R^1 can be optionally substituted aryl. This disclosure does not have the specificity to anticipate Applicants' claims. Additionally, the detailed description does not provide guideposts for arriving at compounds encompassed by Applicants' claims. Tsutomu *et al.* describe at page 1, lines 15-24, that "R^1 is . . . aryl which may bear one or more substituent(s) selected from the group of halogen, hydroxy, nitro, amino, di(lower)alkylamino, lower alkoxy and ar(lower)alkoxy." In none of the 1,2-dihydropyrimidine derivatives purportedly disclosed by Tsutomu *et al.* is the substituent R^1 an optionally substituted phenyl linked to an optionally substituted phenyl by one of –O-, -S-, -NH-, or $–CH_2$-. Additionally, claims 1 and 63 of the present application require that when Y is R_7, i.e., when Applicants' X-Y is optionally substituted alkyl linked to the phenyl ring directly or by one of –O-, -S-, -NH-, or $–CH_2$-, Applicants' R_1 is aminocarbonyl. Tsutomu *et al.* do not disclose any compounds in which both (i) R^1 (which corresponds to Applicants' X-Y) is optionally substituted alkyl linked to the phenyl ring directly or by one of –O-, -S-, -NH-, or $–CH_2$-, and (ii) a substituent which corresponds to Applicants' R_1 is aminocarbonyl.

Regarding compounds of formulae (IIa), (IIb), (IIc), and (IId) of Tsumotu *et al.*, none of the formulae describe any compound embraced by Applicants' claims. In formula (IIa), R^1 is as defined above at page 1, lines 15-24 of Tsumotu *et al.* In view of

the above, compounds of formula (IIa) do not anticipate Applicants' claims. In formula (IIb), (IIc), and (IId), R^1c can only be a nitro-substituted aryl, R^1d can only be an amino-substituted aryl, and R^1e can only be an aryl substituted with di(lower)alkylamino, respectively. None of these groups is an optionally substituted phenyl linked to an optionally substituted phenyl by one of –O-, -S-, -NH-, or $–CH_2$-, or an optionally substituted alkyl linked to the phenyl ring directly or by one of –O-, -S-, -NH-, or $–CH_2$-. Therefore, Applicants' claims are not anticipated by any compound of formulae (IIa), (IIb), (IIc), and (IId) of Tsumotu *et al.*

For the same reasons, Tsutomu *et al.* do not disclose a pharmaceutical composition as claimed in claim 50 or claim 68. Thus, Tsutomu *et al.* do not teach each and every element of claims 1, 50, 63, and 68 and, therefore, Tsutomu *et al.* do not anticipate claims 1, 50, 63, or 68 or any claim dependent on these claims.

In view of the above, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) of claims 1, 50-51, and 61-68 are respectfully requested.

Rejection under 35 U.S.C. § 103(a)

Applicants acknowledge with appreciation that the Examiner has withdrawn the rejections under 35 U.S.C. § 103(a) over Rorig *et al.* (U.S. Pat. No. 3,149,109) and Terada *et al.* (U.S. Pat. No. 5,405,553).

The Examiner has rejected claims 1-3, 6, 8-11, 14-15, 17-19, 21-25, 50-51, and 61-68 under 35 U.S.C. § 103(a) as allegedly being unpatentable over El-Kafrawy *et al.* (*J. Chem. Soc. Pak. 14(1)*:59-66 (1992)). Applicants respectfully traverse this rejection.

The Examiner's rejection is the same as made in the previous Office Action. The Examiner's reasons are as follows:

> Applicants argue that the compounds taught are dihydro compounds which is incorrect. See page 63, compounds 6a-6e. Furthermore, the fact that the compounds showed variation in activity does not negate motivation as it is expected in the art.

(Office Action, page 5, lines 4-7).

Applicants respectfully disagree. Applicants respectfully submit that the Examiner has failed to establish *prima facie* case of obviousness. El-Kafrawy *et al.* do not teach or suggest all the claim limitations and, furthermore, teach away from the present invention as argued in response to the previous Office Action.

As stated earlier, compounds 4a-4h, including compounds 4a-4c, of El-Kafrawy *et al.* do not include a pyrimidine ring as required by the claims of the present invention as amended, but a partially hydrogenated pyrimidine ring. Furthermore, compounds 4a-4c include a hydrazino group and neither of the substituents R_1 and R_2 in the present claims are defined as hydrazino or any other group taught by compounds 4d-4h. Thus, compounds 4a-4c do not teach or suggest all the claim limitations.

Referring to the arguments made in the previous reply, Applicants respectfully submit that the teaching of El-Kafrawy *et al.* would have been ambiguous for a person skilled in the art at the time the present invention was made with regard to compounds 5a and 5b, even in view of compounds 6a-6e described at page 63 of the reference.

In order to expedite the prosecution of the present application, Applicants have amended claim 1 by adding a proviso requiring that each R_2 is hydrogen when R_1 is carboxy, X is O, A_1 is N, and Y is an optionally substituted phenyl group. Support for this amendment is found in the examples of the original specification where the only prepared pyrimidine compound that has a carboxy group in the 2-position of the pyrimidine ring does not have any other substituent attached to the pyrimidine ring other than an optionally substituted phenyl-O-phenyl (*See* Example 1d in paragraph [0157] at page 43 of the specification as filed). Claim 2 has been amended accordingly by adding a proviso requiring that each R_2 is hydrogen when R_1 is carboxy, X is O, and A_1 is N. Claim 50, directed to a pharmaceutical composition has been amended according to claim 1. Furthermore, claims 63 and 68 have been amended to read as independent claims, and by deleting the terms "alkylcarbonylamino" and "arylcarbonylamino" from the definitions for R_2 to further distinguish compounds of the present invention from

compounds 6a-6e of El-Kafrawy *et al.* Applicants wish to point out that neither claim 63 nor claim 68 include "amino" as a definition for R_2.

It is respectfully submitted that there is no teaching or suggestion in El-Kafrawy *et al.* for a person skilled in the art at the time of the invention was made to prepare pyrimidine compounds as claimed in claims 1, 2, and 63, as amended, or any claim dependent on these claims, wherein Y is an optionally substituted phenyl with a reasonable expectation of success. For the same reason, it is respectfully submitted that there is no teaching or suggestion in El-Kafrawy *et al.* for a person skilled in the art at the time of the invention was made to prepare pharmaceutical compositions as claimed in claims 50 or 68, as amended, or any claim dependent on these claims, with a reasonable expectation of success.

As stated in reply to the previous Office Action, compound 5b of El-Kafrawy *et al.* includes a 3,4-dichlorophenyl group attached to the alleged pyrimidine ring and the 4-Cl substituent in compound 5b corresponds to the substituent Y-X- of Formula I of the present invention where X is absent, i.e., the 4-Cl-substituent corresponds to R_7 of Formula I of the present invention. Independent claims 1 and 63 require that R_7 is "optionally substituted alkyl" and that when Y is R_7 then R_1 is aminocarbonyl. This is neither taught nor suggested by El-Kafrawy *et al.* Thus, El-Kafrawy *et al.* do not teach or suggest all the claim limitations. It is respectfully submitted that there is no teaching or suggestion in El-Kafrawy *et al.* for a person skilled in the art to modify compound 5b in a way to reach compounds of Formula I of the present invention where Y is R_7 with a reasonable expectation of success.

In view of the above, it is respectfully submitted that there is no suggestion or motivation in El-Kafrawy *et al.* for one of ordinary skill in the art to prepare the compounds or pharmaceutical compositions as claimed in claims 1-3, 6, 8-11, 14-15, 17-19, 21-25, 50-51, and 61-68 of the present invention with a reasonable expectation of success. Therefore, it would not have been obvious to one skilled in the art at the time

the invention was made to expect instant compounds to possess the utility taught by El-Kafrawy *et al.*

Claim 61 is directed to a pharmaceutical composition comprising a compound as claimed in claim 59 or claim 60. It is respectfully submitted that the Examiner has found claims 59 and 60 allowable and, thus, the rejection of claim 61 was in error and should be withdrawn.

In view of the above, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) of claims 1-3, 6, 8-11, 14-15, 17-19, 21-25, 50-51, and 61-68 are respectfully requested.

Objections and Allowable Subject Matter

The Examiner has objected to claims 39 and 59-60 as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Applicants respectfully traverse this objection. In view of the above arguments, Applicants submit that the rejections have been rendered moot and that the claims are patentable in view of the references cited by the Examiner. Reconsideration and withdrawal of the objection to claims 39 and 59-60 are respectfully requested.

Applicants note with appreciation that the Examiner has found claims 39 and 59-60 allowable since specific species embraced in this claim are not taught or suggested by the art of record or from a search in the relevant art area.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. In view of the foregoing remarks, Applicants submit that the claimed

invention, as amended, is neither anticipated nor rendered obvious in view of the prior art references cited against this application.

Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

John M. Covert
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SKGF_DC1:73949.1

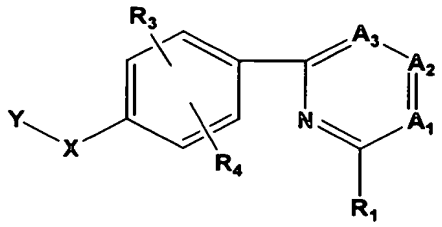
Version with markings to show changes made

In the Claims:

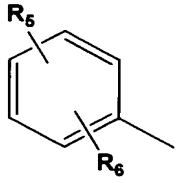
New claims 69-71 have been added.

Claims 1, 2, 50, 51, 63, and 68 have been amended as follows:

1. (Twice Amended) A compound having the Formula I:



or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

Y is 

or R_7,

provided that when Y is R_7, R_1 is aminocarbonyl;

A_1 is N and A_2 and A_3 are CR_2, or A_3 is N and A_1 and A_2 are CR_2;

R_1 is selected from the group consisting an optionally substituted alkyl, amino, alkylthio, $C(O)R_8$, SO_2R_8, $OC(O)NH_2$, 2-imidazolinyl, 2-imidazolyl, 3-pyrazolyl, 5-isoxazolyl, and 3-(1,2,4)-triazolyl;

each R_2 is selected from the group consisting of hydrogen, optionally substituted alkyl, alkenyl, or alkynyl, halogen, hydroxy, cycloalkyl, cyano, amino, alkylamino, dialkylamino, alkoxy, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, and aralkylcarbonylamino; or R_1 and R_2 are taken together with the carbon atoms to which they are attached to form a heterocyclic ring;

R_3, R_4, R_5, and R_6 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, halogen, haloalkyl, hydroxyalkyl, hydroxy, nitro, amino, cyano, amide, carboxyalkyl, alkoxyalkyl, ureido, acylamino, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol;

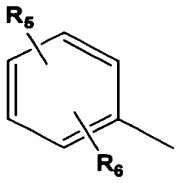
R_7 is an optionally substituted alkyl;

R_8 is selected from the group consisting of alkyl, alkenyl, alkynyl, OR_9, amino, alkylamino, dialkylamino, alkenylamino, dialkylaminoalkenyl, dialkylaminoalkylamino, dialkylaminoalkenylamino, alkylaminoalkenyl-amino, hydroxyaminoalkenylamino, cycloalkyl, heterocycloalkyl, cycloalkylalkylamino, heterocycloalkylamino, aryl, arylalkyl, arylalkenyl, arylalkynyl, and arylalkylamino, all of which can be optionally substituted, provided that R_8 is not OR_9 when R_1 is SO_2R_8; wherein

R_9 is selected from the group consisting of hydrogen, optionally substituted alkyl, and an alkali metal; and

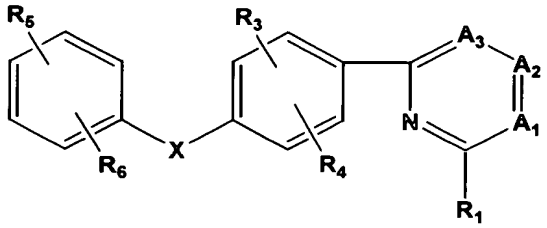
X is one of O, S, NH, or CH_2 when Y is other than R_7; or

X is one of O, S, NH, CH_2 or absent when Y is R_7;

with the [proviso] provisos that R_2 is not methoxy if R_5 is trifluoromethyl, R_6 is H, X is O and R_1 is SO_2CH_2Ph; or each R_2 is hydrogen when R_1 is carboxy, X is O, A_1 is N, and Y is 

.

2. (Twice Amended) A compound having the Formula II:



or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

A_1 is N and A_2 and A_3 are CR_2, or A_3 is N and A_1 and A_2 are CR_2;

R_1 is selected from the group consisting an optionally substituted alkyl, amino, alkylthio, $C(O)R_8$, SO_2R_8, $OC(O)NH_2$, 2-imidazolinyl, 2-imidazolyl, 3-pyrazolyl, 5-isoxazolyl, and 3-(1,2,4)-triazolyl;

each R_2 is selected from the group consisting of hydrogen, optionally substituted alkyl, alkenyl, or alkynyl, halogen, hydroxy, cycloalkyl, cyano, amino, alkylamino, dialkylamino, alkoxy, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, and

aralkylcarbonylamino; or R_1 and R_2 are taken together with the carbon atoms to which they are attached to form a heterocyclic ring;

R_3, R_4, R_5, and R_6 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, halogen, haloalkyl, hydroxyalkyl, hydroxy, nitro, amino, cyano, amide, carboxyalkyl, alkoxyalkyl, ureido, acylamino, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol; and

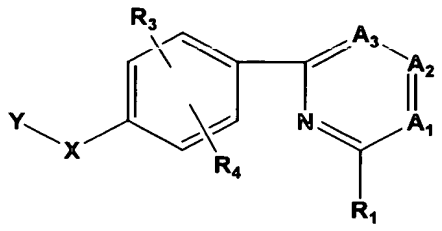
R_8 is selected from the group consisting of alkyl, alkenyl, alkynyl, OR_9, amino, alkylamino, dialkylamino, alkenylamino, dialkylaminoalkenyl, dialkylaminoalkylamino, dialkylaminoalkenylamino, alkylaminoalkenyl-amino, hydroxyaminoalkenylamino, cycloalkyl, heterocycloalkyl, cycloalkylalkylamino, heterocycloalkylamino, aryl, arylalkyl, arylalkenyl, arylalkynyl, and arylalkylamino, all of which can be optionally substituted, provided that R_8 is not OR_9 when R_1 is SO_2R_8; wherein

R_9 is selected from the group consisting of hydrogen, optionally substituted alkyl, and an alkali metal; and

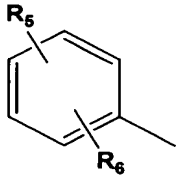
X is one of O, S, NH, or CH_2;

with the [proviso] provisos that R_2 is not methoxy if R_5 is trifluoromethyl, R_6 is H, X is O and R_1 is SO_2CH_2Ph; or each R_2 is hydrogen when R_1 is carboxy, X is O, and A_1 is N.

50. (Twice Amended) A pharmaceutical composition, comprising the compound of formula:



or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

Y is 

or R_7, provided that when Y is R_7, R_1 is

aminocarbonyl;

A_1 is N and A_2 and A_3 are CR_2, or A_3 is N and A_1 and A_2 are CR_2;

R_1 is selected from the group consisting an optionally substituted alkyl, amino, alkylthio, $C(O)R_8$, SO_2R_8, $OC(O)NH_2$, 2-imidazolinyl, 2-imidazolyl, 3-pyrazolyl, 5-isoxazolyl, and 3-(1,2,4)-triazolyl;

each R_2 is selected from the group consisting of hydrogen, optionally substituted alkyl, alkenyl, or alkynyl, halogen, hydroxy, cycloalkyl, cyano, amino, alkylamino, dialkylamino, alkoxy, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, and aralkylcarbonylamino; or R_1 and R_2 are taken together with the carbon atoms to which they are attached to form a heterocyclic ring;

R_3, R_4, R_5, and R_6 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, halogen, haloalkyl, hydroxyalkyl, hydroxy, nitro, amino, cyano, amide, carboxyalkyl, alkoxyalkyl, ureido, acylamino, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol;

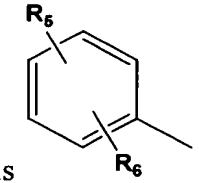
R_7 is an optionally substituted alkyl;

R_8 is selected from the group consisting of alkyl, alkenyl, alkynyl, OR_9, amino, alkylamino, dialkylamino, alkenylamino, dialkylaminoalkenyl, dialkylaminoalkylamino, dialkylaminoalkenylamino, alkylaminoalkenyl-amino, hydroxyaminoalkenylamino, cycloalkyl, heterocycloalkyl, cycloalkylalkylamino, heterocycloalkylamino, aryl, arylalkyl, arylalkenyl, arylalkynyl, and arylalkylamino, all of which can be optionally substituted, provided that R_8 is not OR_9 when R_1 is SO_2R_8; wherein

R_9 is selected from the group consisting of hydrogen, optionally substituted alkyl, and an alkali metal; and

X is one of O, S, NH, or CH_2 when Y is other than R_7; or

X is one of O, S, NH, CH_2 or absent when Y is R_7;

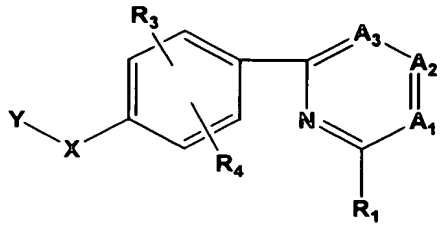
with the proviso that each R_2 is hydrogen when R_1 is carboxy, X is O, A_1 is N, and Y is 

;

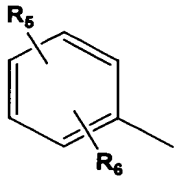
and a pharmaceutically acceptable carrier or diluent.

51. (Twice Amended) The composition of claim 50, wherein the compound is as claimed in any one of claims 1, [or] 2, 63, or 69.

63. (Once Amended) A compound [of claim 1] having the Formula I:



or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

Y is  or R_7,

provided that when Y is R_7, R_1 is aminocarbonyl;

A_1 is N and A_2 and A_3 are CR_2; or A_3 is N and A_1 and A_2 are CR_2;

R_1 is selected from the group consisting an optionally substituted alkyl, amino, alkylthio, $C(O)R_8$, SO_2R_8, $OC(O)NH_2$, 2-imidazolinyl, 2-imidazolyl, 3-pyrazolyl, 5-isoxazolyl, and 3-(1,2,4)-triazolyl;

each R_2 is selected from the group consisting of hydrogen, optionally substituted alkyl, alkenyl, or alkynyl, halogen, hydroxy, cycloalkyl, cyano, alkylamino, dialkylamino, alkoxy, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, [alkylcarbonylamino, arylcarbonylamino,] and aralkylcarbonylamino; or R_1 and R_2 are taken together with the carbon atoms to which they are attached to form a heterocyclic ring;

R_3, R_4, R_5, and R_6 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, halogen, haloalkyl, hydroxyalkyl, hydroxy, nitro, amino, cyano, amide, carboxyalkyl, alkoxyalkyl, ureido, acylamino, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol;

R_7 is an optionally substituted alkyl;

R_8 is selected from the group consisting of alkyl, alkenyl, alkynyl, OR_9, amino, alkylamino, dialkylamino, alkenylamino, dialkylaminoalkenyl, dialkylaminoalkylamino, dialkylaminoalkenylamino, alkylaminoalkenyl-amino, hydroxyaminoalkenylamino,

cycloalkyl, heterocycloalkyl, cycloalkylalkylamino, heterocycloalkylamino, aryl, arylalkyl, arylalkenyl, arylalkynyl, and arylalkylamino, all of which can be optionally substituted, provided that R_8 is not OR_9 when R_1 is SO_2R_8; wherein

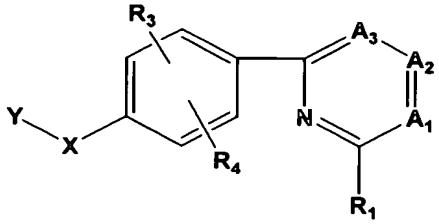
R_9 is selected from the group consisting of hydrogen, optionally substituted alkyl, and an alkali metal; and

X is one of O, S, NH, or CH_2 when Y is other than R_7; or

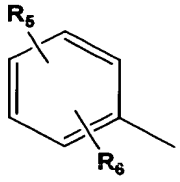
X is one of O, S, NH, CH_2 or absent when Y is R_7;

with the proviso that R_2 is not methoxy if R_5 is trifluoromethyl, R_6 is H, X is O and R_1 is SO_2CH_2Ph.

68. (Once Amended) A pharmaceutical composition [of claim 50], comprising the compound of formula:



or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

Y is 

or R_7, provided that when Y is R_7, R_1 is aminocarbonyl;

A_1 is N and A_2 and A_3 are CR_2; or A_3 is N and A_1 and A_2 are CR_2;

R_1 is selected from the group consisting an optionally substituted alkyl, amino, alkylthio, $C(O)R_8$, SO_2R_8, $OC(O)NH_2$, 2-imidazolinyl, 2-imidazolyl, 3-pyrazolyl, 5-isoxazolyl, and 3-(1,2,4)-triazolyl;

each R_2 is selected from the group consisting of hydrogen, optionally substituted alkyl, alkenyl, or alkynyl, halogen, hydroxy, cycloalkyl, cyano, alkylamino, dialkylamino, alkoxy, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, [alkylcarbonylamino, arylcarbonylamino,] and

aralkylcarbonylamino; or R_1 and R_2 are taken together with the carbon atoms to which they are attached to form a heterocyclic ring;

R_3, R_4, R_5, and R_6 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, halogen, haloalkyl, hydroxyalkyl, hydroxy, nitro, amino, cyano, amide, carboxyalkyl, alkoxyalkyl, ureido, acylamino, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol;

R_7 is an optionally substituted alkyl;

R_8 is selected from the group consisting of alkyl, alkenyl, alkynyl, OR_9, amino, alkylamino, dialkylamino, alkenylamino, dialkylaminoalkenyl, dialkylaminoalkylamino, dialkylaminoalkenylamino, alkylaminoalkenyl-amino, hydroxyaminoalkenylamino, cycloalkyl, heterocycloalkyl, cycloalkylalkylamino, heterocycloalkylamino, aryl, arylalkyl, arylalkenyl, arylalkynyl, and arylalkylamino, all of which can be optionally substituted, provided that R_8 is not OR_9 when R_1 is SO_2R_8; wherein

R_9 is selected from the group consisting of hydrogen, optionally substituted alkyl, and an alkali metal; and

X is one of O, S, NH, or CH_2 when Y is other than R_7; or

X is one of O, S, NH, CH_2 or absent when Y is R_7; and a pharmaceutically acceptable carrier or diluent.